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Idiopathic Immune-Mediated Acquired von Willebrand's Disease in a Patient With Angiodysplasia: Demonstration of an Unusual Inhibitor Causing a Functional Defect and Rapid Clearance of von Willebrand Factor

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A case of idiopathic immune-mediated von Willebrand's disease (AvWD) associated angiodysplasia and recurrent lower gastrointestinal bleeding is reported. Coagulation parameters at presentation were activated partial thromboplastin time of 41 sec, bleeding time >15 min, factor VIII procoagulant activity, 5%; von Willebrand factor antigen (WF:Ag) 5%, and vWF:ristocetirn cofactor activity 11% sodium dodecyl sulfate-agarose gel electrophoresis pattern of plasma vWF showed a pattern similar to type II vWD. An in vitro inhibitor against vWF in the immunoglobulin (Ig)G fraction of the patient's plasma was demonstrated vWF parameters showed a short-lived increase after 1-deamino-8-D-arginine vasopressin (DDAVP) administration. The patient's bleeding episodes were initially managed adequately with cryoprecipitate replacement therapy and DDAVP, to which she became refractory. No significant improvement was achieved following the institution of immunosuppressive therapy in the form of high-dose steroids and cyclophosphamide. She was then treated with intravenous immunoglobulin (Ivlg) to which she showed an adequate response in terms of her clinical situation and her hemostatic parameters. The patient is on maintenance treatment with repeated courses of Ivlg based on vWF parameter monitoring. To our knowledge, this is the third reported association between idiopathic immune-mediated AvWD and angiodysplasia. Am. J. Hematol. 60: 151–157, 1999. © 1999 Wiley-Liss, Inc.

Key words: acquired von Willebrand's disease; angiodysplasia; intravenous immunoglobulin

INTRODUCTION

von Willebrand factor (vWF) is a large molecular weight glycoprotein that is present in plasma as a series of multimers that range in molecular weight from 800,000 to 12,000,000 dalton. It is synthesized by endothelial cells from which it is released into circulation and incorporated into the subendothelial matrix, and by megakaryocytes, which package it into alpha granules of platelets for release at the time of activation. The factor VIII (FVIII): vWF complex exists only in the circulation; thus vWF in the subendothelium or inside platelets does not carry FVIII. Normal hemostasis requires vWF for two functions: 1. to support formation of the hemostatic plug through adhesion and aggregation of platelets at sites of vascular injury; and 2. to act as a carrier for FVIII, thus prolonging the half-life of this procoagulant in the circulation.

A qualitative and/or quantitative deficiency of vWF may result in a bleeding tendency. Apart from inherited

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von Willebrand's disease (IvWD), acquired causes of von Willebrand's disease (AvWD) have been described. They have been reported in the literature to be associated with lymphoproliferative disorders [1–7], myeloproliferative disorder [8–10,12,13], or autoimmune disorder [14,15]. It has also been reported in cases of thalassemia [16], monoclonal gammopathy of undetermined significance (MGUS) [17–22], Wilm's tumor [23,24], adrenal cortical carcinoma [25], hypothyroidism [26,27], angiodysplasia [28–34], certain cardiac or vascular defects [35], and in association with drugs such as valproic acid [36], ciprofloxacin [37], griseofulvin [38], and hydroxy ethyl starch (HES) [39,40]. There have been isolated reports of AvWD in a patient following bone marrow transplantation [41], in a patient with excessive fibrinolysis of unclear etiology [42], and in a patient with hemophilia A following high-dose infusion of FVIII [43].

AvWD closely resembles IvWD in terms of its clinical features and laboratory findings. In the majority of the reported patients with AvWD, the mechanism of the vWF deficiency has not been described clearly. Various pathogenic mechanisms have been postulated. The most commonly seen in an autoantibody, usually immunoglobulin (Ig) G class, directed against the FVIII-vWF complex that either inactivates its biological activities, or forms an immune complex with vWF which is rapidly cleared from the circulation.

This report describes an interesting case of an AvWD similar to type II IvWD that is associated with angiodysplasia. No underlying immune disorder or malignancy was detected during six years of follow-up. In vitro inhibition studies demonstrated the presence of an autoantibody against vWF in the patient's plasma that actually inhibited its function as expressed by low ristocetin cofactor activity (RiCof).

CASE REPORT

A 65-year-old white woman was admitted to the hospital in 1991 with abdominal pain and rectal bleeding. She had no history of abnormal bleeding during each of her four deliveries or during various dental procedures. She did, however, have a two-year history of bruising. There was no clinical evidence of lymphoproliferative or autoimmune disorders, and she was taking no medications. Except for third-degree hemorrhoids, her past medical history was unremarkable. Family history revealed no members with known bleeding disorders. On examination, she appeared slightly pale and there were few scattered generalized petechiae. Hemoccult test was positive. Other physical findings were unremarkable.

The initial blood count revealed a normal hemoglobin level, and normal white blood cell and platelet counts. Initial coagulation results revealed a normal international normalized ratio (INR), a prolonged activated thromboplastin time (APTT), and a prolonged Ivy bleeding time. At presentation, FVIII procoagulant activity (FVIII:C), vWF antigen (vWF:Ag), and ristocetin cofactor (vWF:RiCof) activity were markedly reduced. Multimeric analysis of the patient's vWF showed a pattern similar to type II IvWD with high molecular weight multimers lacking and some intermediate multimers reduced. Further analysis using a high-resolution gel demonstrated normal low molecular weight multimers. Serum protein electrophoresis and bone marrow aspirate and trephine biopsy were normal. The patient's mother and one of her daughters were tested and showed no hemostatic abnormalities. The patient's father was decreased, and her remaining three children were unavailable for testing.

The bleeding episode stopped spontaneously with no further intervention. However, over the following years she had recurrent lower gastrointestinal bleeding episodes which were unpredictable and of variable severity, requiring frequent admissions and necessitating frequent administrations of 1-deamino-8-D-arginine vasopressin (DDAVP) and replacement with packed red blood cells and cryoprecipitate. Several repeated endoscopic gastrointestinal examinations demonstrated the presence of multiple colonic angiodysplastic lesions in the cecum and sigmoid colon, a few of which were accessible for thermocoagulation. In 1993 the patient underwent hemorrhoidectomy during which adequate hemostasis was achieved by DDAVP. However, the half-life of her plasma vWF following DDAVP treatment was only 4 hr (normal range, 8–12 hr) [6,13,44], which indicated a rapid rate of clearance. This suggested the presence of a vWF inhibitor. Subsequently, anti-vWF antibodies were detected in the patient's plasma.

Initially, her recurrent bleeding episodes responded adequately to DDAVP treatment and cryoprecipitate therapy; however, she became refractory to these measures and was subsequently started on high-dose steroid therapy (prednisone 20 mg/day) as a measure of immunosuppression. She continued to have bleeding episodes whenever the dose was tapered down. A trial for several weeks with cyclophosphamide (100 mg/day) was started, but without significant improvement in her bleeding situation or laboratory parameters. An alternative treatment modality with intravenous immunoglobulin (IvIg) was instituted (25 g/day for two days) on a monthly basis to which she continues to have a good response. This therapy raises the RiCof activity to ~50% and over the course of the month it falls back to ~25% at which time the IvIG treatment is repeated. No further episodes of frank bleeding have occurred since initiating this treat-

ment regimen. No underlying immune disorder or malignancy was detected during six years of close follow-up.

MATERIALS AND METHODS

Blood Sampling and Coagulation Tests

Blood was anticoagulated in sodium citrate (Vacutainer tube, Becton-Dickinson, Mississauga, ON). Complete blood count was carried out on EDTA-anticoagulated blood on a Coulter Counter IV Plus (Hialeah, FL). Prothrombin time and APTT were performed using the ACL system and General Diagnostic reagents (Organon Teknika, Scarborough, ON). The bleeding time was measured by the modified method of Ivy using a plastic template (Simplate, Organon Teknika). Standard one-stage assay was performed for FVIII:C using FVIII deficient plasma (George King Biomedical, Overland Park, KS). Immunological determinations of vWF:Ag were made using an enzyme-linked immunosorbent assay (ELISA) method (Diagnostica Stago, Guelph, ON) and the Laurell technique. vWF:RiCof was assayed as described elsewhere [45]. Plasma mixing studies were performed by incubating 1 part patient plasma with 3 parts normal pool then assessing the vWF:RiCof activity. Plasma for vWF multimer analysis was collected in sodium citrate and in EDTA on two separate occasions to rule out the possibility of anticoagulant-related artifacts. The multimeric composition of vWF was analyzed by sodium dodecyl sulfate (SDS)-agarose gel electrophoresis. The subunit composition of vWF was analyzed by immunoblotting with anti-vWF monoclonal antibodies and ^{125}I-rabbit anti-mouse antibody. Following the demonstration of an abnormal pattern in this analysis, a high-resolution gel analysis was performed to assess the low molecular weight multimers.

Identification of Anti-vWF Autoantibody

IgG was isolated from patient plasma or pooled normal donor plasma (NP) by affinity chromatography using Protein G-Sepharose (Pharmacia, Baie d'Urfe, Que). Fractions collected from chromatography were assessed for protein concentration using the BioRad protein assay and for purity using SDS-polyacrylamide gel electrophoresis. Fractions containing pure IgG were pooled and dialyzed against phosphate-buffered saline, pH 7.4, containing 0.2% sodium azide. All IgG preparations were stored at 4°C.

To examine the effect of patient IgG on vWF in normal plasma, NP was incubated with an equal volume of either patient IgG or NP IgG at 6 mg/ml for 60 min at room temperature. Each mixture was then passed through a Protein G-Sepharose and the column eluant tested for vWF level using a von Willebrand reagent agglutination assay (Behringwerke, Montreal, Que). To establish the degree of sample dilution produced by the chromatography, albumin levels were assessed in treated and untreated plasma samples before and after chromatography. The entire experiment was performed on two occasions.

To determine whether an autoantibody was present that was directed against the FVIII bound to vWF, an APTT-based FVIII assay was performed as follows: Plasma-derived human FVIII (Bayer, Etobicoke, ON) at 1 U/ml was incubated with an equal volume of either patient IgG or NP IgG at 6 mg/ml for 60 min at room temperature. Dilutions of this mixture at a final FVIII content of 5%, 10%, and 20% of normal were incubated with FVIII deficient plasma (Pacific Hemostasis, Charlotte, NC) and assessed in an APTT assay (Organon Teknika).

TABLE I. Initial Evaluation at Presentation*

Test	Result	Reference range
Platelet count	228 × 10^9/L	140–350 × 10^9/L
PT (sec)/INR	13/1.1	10–13/0.9–1.1
APTT	41.0 sec	24–37 sec
Bleeding time	>15	4–8 sec
vWF Ag	8%	50–150%
vWF:RiCof	11%	50–150%
FVIII:C	5%	50–150%

*PT, prothrombin time; INR, international normalized ratio; APTT, activated thromboplastin time; vWF:Ag, von Willebrand factor antigen; vWF:RiCof, von Willebrand factor ristocetin cofactor activity; FVIII:C, factor VIII procoagulant.

RESULTS

Initial coagulation data at presentation are shown in Table I. The levels of FVIII:C and vWF parameters are consistent with a diagnosis of vWD. vWF:Ag was only detectable by the ELISA method with no precipitation detectable by the Laurell technique. Simple plasma mixing studies showed that an incubation of 1 part patient's plasma with 3 parts normal pooled plasma contained vWF:RiCof activity of 30% rather than the expected level of 75%. Table II shows the results of FVIII:C and vWF measurements before and after DDAVP.

The multimer pattern of the patient's plasma vWF at presentation showed that the intensity of vWF multimers was markedly reduced and the high molecular weight multimers (HMWM) were undetectable in EDTA plasma specimens. A secondary analysis using a high-resolution gel to visualize the low molecular weight multimers showed that these forms of vWF were normal.

The effect of exposure of NP to patient IgG was assessed by prolonged incubation of NP with purified IgG samples from the patient or from normal pooled plasma followed by measurement of vWF levels. The vWF level

TABLE II. FVIII and vWF Measurements Before and After DDAVP Infusion*

Time	FVIII:C %	vWF:Ag (%)	vWF:RiCof (%)
Before	5	8	11
30 min	182	71	90
4 hr	48	37	24

*FVIII, factor VIII; vWF, von Willebrand factor; DDAVP, 1-deamino-8-D-arginine vasopressin; FVIII:C, factor VIII procoagulant; vWF:Ag, von Willebrand factor antigen.

TABLE III. Effect of Exposure of FVIII to Patient or Normal IgG on FVIII Function in an APTT Assay Using FVII-Deficient Plasma*

FVIII level added (% of normal)	APTT (sec) in the presence of IgG	
	Patient IgG	Normal IgG
20	58	59
10	62	65
5	70	73

*FVIII, factor VIII; IgG, immunoglobulin G, APTT, activated thromboplastin time.

in the starting NP was 84%. Following incubation with NP IgG and chromatography on Protein G-Sepharose the vWF level fell to 62% owing to the dilutional effect of the chromatography step. However, incubation of NP with patient IgG and subsequent chromatography on Protein G-Sepharose dropped the detectable vWF to 39%. This experiment was repeated a second time with similar results: starting plasma vWF was 83%, incubation with normal IgG prior to chromatography gave a 66% vWF level, and incubation with patient IgG prior to chromatography lowered the vWF level to 32%. Since the Protein G-Sepharose column is highly specific for Ig, particularly IgG, this observation suggested the presence of a vWF-reactive antibody in the patient's plasma. In one experiment, all plasma samples were also analyzed for vWF:RiCof activity. Untreated plasma had 90% vWF:Ricof activity; samples treated with normal IgG or patient IgG prior to chromatography contained 71% and 40% vWF:RiCof activity, respectively.

To exclude the possibility that the autoantibody was actually directed against the FVIII molecule in the vWF-FVIII complex, the ability of isolated IgG to interfere with the detection of known amounts of FVIII was assessed. Fractionated human FVIII was exposed to patient IgG or NP IgG and FVIII level assessed. No difference was seen at any concentration tested (Table III). These data suggested that the autoantibody was directed against vWF and not FVIII.

DISCUSSION

AvWD is a rare entity. It usually describes a late-onset bleeding diathesis with a negative family history of bleeding tendency. The majority of the reported patients with this disorder have underlying autoimmune or lymphoproliferative disorders with or without monoclonal gammopathies, which strongly suggests that this entity has an immunologic basis. However, there are cases in which the underlying disease has no obvious relationship to any abnormality of the immune system (e.g., angiodysplasia, myeloproliferative disorders). Among the reported cases that are presumably caused by an immune mechanism, in vitro demonstration of an inhibitor directed against vWF was present in only a minority of cases.

In this report, our patient has an acquired bleeding disorder that is similar to type II IvWD as indicated by her clinical and laboratory features. Following IvIg therapy, her vWF parameters normalized indicating that her vWF deficiency was not congenital. Our investigation of the mechanism underlying the AvWD revealed compelling evidence for the presence of an inhibitor: First, the demonstration of an in vitro inhibitory effect of the IgG fraction of the patient's plasma against vWF:Ag and vWF:RiCof without interfering with FVIII:C; second, the rapid clearance rate of her plasma vWF following DDAVP administration; and third, correction of vWF laboratory parameters following treatment with IvIg.

Most studies have shown that the classic diagnosis of immune-mediated AvWD is difficult, since the inhibitor is infrequently detected in traditional mixing studies. However, as demonstrated by several investigators [46,47], we were able to demonstrate the presence of a specific inhibitor against vWF that was contained in the patient's immunoglobulin fraction, as indicated by its ability to reduce vWF:Ag as well as ristocetin-induced platelet agglutination. The inhibitor had no significant activity against FVIII:C. This observation is consistent with the data reported in the literature, regarding the specificity of autoantibodies in AvWD [40,44].

In our patient, unlike most published reports, the presence of an anti-vWF autoantibody was detected in vivo, as indicated by the rapid clearance of plasma vWF following the administration of DDAVP. Thus, it appears that the antibody bound to or near the active site on vWF, as defined by vWF:RiCof, and still caused rapid clearance in vivo, a phenomenon that has been rarely observed.

Several studies have evaluated plasma vWF clearance data by comparing the effect of DDAVP in AvWD and IvWD on the assumption that this agent should amplify the pathologic mechanisms for releasing vWF from cellular compartments and clearing it from plasma [6,13,44]. In AvWD, DDAVP infusion produces a marked increase in vWF:Ag, vWF:RiCof, and FVIII:C soon after, and HMWM, possibly released from cellular

compartments, appeared transiently in the circulation; in most studies these are preferentially cleared for an unknown reason. This observation is similar to that of patients with IvWD type I, but differs in that the increase was of lesser magnitude and more short-lived.

The interesting observation that vWF:Ag was undetected by Laurell immunoelectrophoresis assay and was detected by the ELISA technique, could be related to the sensitivity of the assay, the specificity of the monoclonal antibody used in the assay, or the inability of the monoclonal antibody to recognize its antigenic epitope in the presence of the autoantibody. This observation points out a potential unreliability of the Laurell technique in the work-up of AvWD.

Several interesting points are of note when vWF inhibitors in AvWD are compared with FVIII inhibitors in acquired hemophilia A. First, low FVIII:C levels have been rarely described in association with AvWD [13]. However, in some instances, acquired FVIII inhibitors have impaired ristocetin-induced agglutination of normal platelets, and a few studies have also suggested partial inactivation of vWF [48,49]. Second, limited data are available regarding the kinetics of inhibitors in AvWD; however, unlike FVIII inhibitors which usually exhibit a complex reaction kinetics (type II kinetics), it appears from the available data that vWF inhibitors are heterogeneous group of inhibitors that have in common the characteristic feature of an immediate-acting antibody. Such information on reaction kinetics may be important for appropriate management of patients with AvWD. Third, acquired vWF inhibitors occur most frequently in association with other underlying disorders unlike acquired FVIII inhibitors that are most often of idiopathic origin. When occurring outside the setting of FVIII replacement therapy for hemophilia, both disorders occur predominantly in elderly patients with very few young patients being reported [14,50].

The association of gastrointestinal vascular dysplasia with both the inherited and acquired forms of vWF has been reported. Abnormalities have included diffuse gastrointestinal telangiectasia, similar to those seen in hereditary hemorrhagic telangiectasia, as well as angiodysplasia consisting of small, tortuous, thin-walled blood vessels [29]. It is not clear, however, whether the occurrence of angiodysplasia in vWD is a mere coincidence or has a causal relationship. In an international survey, the prevalence of angiodysplasia in AvWD was found to be 11.7% [51]. To our knowledge, seven cases of immune-mediated AvWD with angiodysplasia have been described [28–30,31–34]. An autoimmune disorder, monoclonal gammopathy, and lymphoproliferative disorder were associated with five patients. No underlying disorder was associated with the remaining two cases [29,33]. Therefore, this is the third reported association between idiopathic immune-mediated AvWD and angiodysplasia of the intestinal tract.

Our case represents a treatment model for immune-mediated AvWD in which all modalities of therapy have been used. The treatment of AvWD is initially directed toward treatment of the underlying disease process and the mechanisms responsible for the development of the syndrome. However, treatment of the underlying disorder may not always be possible or may require surgery, which poses a challenge to an already compromised hemostatic system. In immune-mediated AvWD, adequate hemostasis may be achieved with replacement therapy with coagulation FVIII/vWF concentrate, Humate P, or DDAVP, however, such measures are frequently ineffective due to the rapid clearance of vWF [17,21,52]. In most cases they transiently increase vWF levels and vWF:RiCof which then decrease within 2–3 hr. Immunosuppressive agents including prednisone and cyclophosphamide have been used with limited success [19]. Extracorporeal immunoadsorption was attempted in one patient with short-term success [53]. Consistent with our findings, there have been many reports of successful IvIg infusion for AvWD [17,20–22,47,54]. The mechanism is unknown, but might be related to an effect of IvIg on the clearance of vWF-antibody complexes. The duration of vWF:RiCof normalization after IvIg is highly variable; most reports suggest an effect lasting 10–20 days [55,56]. In general, 0.5–2 g/kg IvIg over 1–2 days produces an immediate and relatively durable effect.

In summary, we have described a patient with idiopathic immune-mediated, IvIg responsive AvWD associated with angiodysplasia. The coagulopathy was associated with the presence of a specific inhibitor to vWF which was demonstrated in vitro as well as in vivo. The case is unusual in view of its idiopathic nature and the activity of the anti-vWF autoantibody as indicated by its ability to impair function and increase clearance of vWF.

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